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Prevalence and Severity of Periodontitis in Indonesian Rheumatoid Arthritis Patients

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Background: Patients with rheumatoid arthritis (RA) may have more prevalent and severe periodontitis than healthy controls. Periodontitis may increase the systemic inflammation in RA.

Aim: To assess periodontitis prevalence and severity, and its potential association with systemic inflammation in Indonesian RA patients.

Methods: A full mouth periodontal examination including probing pocket depth, gingival recession, plaque index and bleeding on probing was performed in 75 Indonesians with RA and 75 age, sex and smoking matched Indonesian controls. A validated questionnaire was used to assess smoking, body mass index, education and medical conditions. In addition, in all participants the use of drugs was noted, and erythrocyte sedimentation rates and serum levels of high sensitivity test c-reactive protein, rheumatoid factor and anti citrullinated protein antibodies were measured. Differences in periodontitis prevalence and 12 measures of periodontitis severity between RA patients and controls were analyzed using univariate analyses.

Result: No significant differences in periodontitis prevalence and 11 measures of periodontitis severity between RA patients and controls were observed. On the other hand, RA patients had a significantly lower surface area of healthy pocket epithelium versus controls ($p=0.008$) and a tendency towards higher high sensitivity c-reactive protein levels was observed in RA patients with severe periodontitis compared to RA patients with no/mild or moderate periodontitis ($p=0.063$). It has to be noted that all RA patients were on anti-inflammatory drugs, while none of the controls used such drugs.

Conclusion: Prevalence and severity of periodontitis in Indonesian RA patients is comparable to controls, but with less healthy pocket epithelium than in controls and a tendency of a higher inflammatory state in RA patients with severe periodontitis.

KEY WORDS:

Periodontitis, Rheumatoid Arthritis, Inflammation, C-Reactive Protein

Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetric inflammation of mainly hand and wrist joints, which leads to permanent deformity and destruction of these joints[1]. RA impairs quality of life and is associated with early mortality. The cause of RA is still unknown.

Studies in Australia, America, Europe and Africa have shown that RA patients have more prevalent and severe periodontitis than non-RA controls when controlling for important confounders like dental plaque, age, sex and smoking[2-9]. Studies in Sweden, Brazil, USA, Turkey, and Japan, however, did not find a higher prevalence and severity of periodontitis in RA patients[10-14]. In other words, the prevalence and severity of periodontitis in RA patients may be influenced by genetic, dietary, cultural and other differences associated with differences in nationality and ethnicity. Although Caucasian, African American, Latin American, North-African and Japanese populations have been studied[2-8, 11], no study has yet been performed in a South East Asian population. Furthermore, the use of non-steroid anti-inflammatory drugs (NSAIDs) and rheumatoid agents in RA patients may affect the pro- and anti-inflammatory cytokine levels in RA patients and thus confound the association between RA and periodontitis[15, 16].

In addition to differences in results due to variations in nationality and ethnicity, the association between RA and periodontitis may also differ because a variety of definitions for periodontitis prevalence and severity has been used. Although various studies have assessed the association between periodontitis and RA[2-16], no study has yet investigated the effect of using several definitions for periodontitis prevalence and severity on the association between periodontitis and RA.

Recently, a few pilot-intervention studies have pointed towards periodontitis as a risk factor for RA[17-20]. After treating periodontitis, a reduction in RA disease activity was shown, possibly related to a reduction in periodontitis associated inflammatory burden. Periodontitis poses an inflammatory burden, as evidenced by increased levels of erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) in RA patients with periodontitis[2-5]. Thus, periodontitis may increase systemic inflammation, which may in turn lead to increase RA severity[21]. Likewise *Helicobacter pylori* infections may contribute to increase RA severity by posing inflammatory burden, while eradication of this bacterium in RA patients improves clinical condition and laboratory markers of RA disease activity[22].

Thus, the aims of this study were to compare periodontitis prevalence and periodontitis severity in Indonesian RA patients with Indonesian age, sex, and smoking matched controls, using a variety of definitions for periodontitis severity[23]. In addition, it was analyzed whether inflammatory burden differed between participants with or without periodontitis, both for RA patients and controls.

PATIENTS AND METHODS

Between July 2008 and February 2009, all consecutive RA patients visiting the Internal Medicine Department of the Dr. Sardjito Hospital Yogyakarta, the Clinic for rheumatology of PKU Muhammadiyah Hospital Yogyakarta, or a private rheumatology clinic in Surabaya, Indonesia that matched the inclusion criteria were informed about the nature of the study and were asked to participate. All RA patients had been diagnosed by rheumatologists (NK and JS) according to revised American College of Rheumatology (ACR) 1987 criteria[1] and were on a regular recall schedule for RA. During the same period, age, sex, and smoking matched

controls were recruited from the consecutive patients that visited the Prof. Soedomo Dental Hospital, Faculty of Dentistry Gadjah Mada University, Yogyakarta for their routine dental check-up. Likewise, these controls were informed about the nature of the study and asked to participate. The inclusion criteria for RA patients and controls were an age ≥18 years and having ≥ 8 remaining teeth. The number of 8 remaining teeth was chosen since there should at least be a minimum periodontitis-associated inflammatory burden, given this inflammatory burden decreases with decreasing number of teeth (e.g. edentulous patients don't have any periodontitis-associated inflammatory burden). Exclusion criteria were presence of other systemic diseases or conditions (e.g diabetes) which are known as risk factors for periodontitis and a history of treatment for periodontal disease. With regard to controls, additional exclusion criteria were the use of medication or consuming drugs which are known to be risk factors for periodontitis[15, 16]. Since no (pilot) data concerning differences between Indonesian RA patients and controls was available we did not perform a formal power analysis. Each RA patient was matched with one control. This study was approved by the Ethical Committee for Research of the Medical Faculty of Gadjah Mada University, Yogyakarta, Indonesia. Informed consent was obtained from all patients and controls.

All participants had to complete a validated general health assessment questionnaire assessing the presence of other diseases and the use of medication. This questionnaire was composed of questions assessing symptoms related to systemic diseases such as heart disease, pulmonary disease, endocrine disorders, hematologic disease, gastro-intestinal disorders, genitourinary disorders and neurological disease, and the use of medications[24]. Information about age, sex, smoking (current and pack years), education level and body mass index (BMI) was obtained by means of a questionnaire.

All participants underwent a full mouth periodontal examination on six sites per tooth assessing probing pocket depth (PD), gingival recession, plaque score, bleeding on probing (BOP) and clinical attachment (CA loss). All permanent fully erupted teeth were examined with a manual periodontal colour coded standard probe[*]. Measurements were made in millimetres and were rounded to the nearest whole millimetre. BOP was recorded as either present or absent within 30 seconds of probing. Plaque score was defined as being present or absent at 6 points on each tooth[2]. The number of missing teeth was also recorded.

Periodontitis prevalence was established according to Page and Eke[23] case definitions. Periodontitis severity was operationalized using a variety of methods (number of sites with PD ≥4, ≥5 and ≥6 mm, number of sites with CA loss ≥3, ≥4, ≥5 and ≥6 mm, mean PD, mean CA loss and percentage of sites with BOP anywhere in the dentition) all currently used to study the association between periodontitis and other diseases[25-27]. To facilitate calculation a freely accessible spreadsheet (www.parsprototo.info; Microsoft Excel 2003 spreadsheet for Windows) was used online. Furthermore, two recently introduced measures of periodontitis severity, the periodontal epithelial surface area (PESA) and the periodontal inflamed surface area (PISA)[28] were calculated, again using the same spreadsheet[†]. PESA reflects the surface area of all pocket epithelium in square millimetres, whereas PISA reflects the surface area of bleeding pocket epithelium in square millimetres. PESA and PISA were calculated using conventional CA loss, gingival recession and BOP measurements. PISA quantifies the surface area of inflamed periodontal tissue in square mm. PISA is a measure of inflammatory burden posed by periodontitis[26, 28].

Finally, a blood sample via vena puncture was taken from all participants (RA patients and controls) to determine c –reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti citrulinated protein antibody (ACPA). High sensitivity CRP (hsCRP) was determined by chemiluminescent enzyme immunoassay[†]. ESR was determined

by Westergren, RF was determined by latex agglutination methods and anti citrullinated protein antibody ACPA was determined by an enzyme link immunosorbent assay[‡].

Statistical Analysis

Data are presented as mean and standard deviation (SD) in case of normal distribution, medians and interquartile range (IQR) in case of non-normal distribution and percentages for categorical data. Since RA patients and controls were matched (age, gender and smoking) differences between RA patients and controls were analyzed using paired sample t-test or in case of a non-normal distribution, Wilcoxon signed rank test and McNemar test. Differences between periodontal status groups within RA patients and controls were analyzed using Kruskall-Wallis (for medians) and Chi-square tests (for percentages), linear by linear association. In case of lack of expected cell count the exact method was used. Statistics were calculated using PASW 18.0.

RESULTS

Prevalence and Severity of Periodontitis in RA Patients and Controls

In total, 75 RA patients (median disease duration 4 years (IQR 2.0; 6.0, range; 1- 15 years) and 75 age, sex, and smoking matched controls were included. All consecutive RA patients and controls that fulfilled the inclusion criteria during the recruiting period agreed to participate in this study. The characteristics of RA patients and controls, including level of education, origin, BMI and medication use are summarized in table 1. Level of education and origin were comparable between RA patients and controls. Mean age, BMI and number of teeth of RA patients were significantly lower than controls whereas plaque score was significantly higher. None of controls used medication, other than birth control pills or antihypertensives. Prevalence and severity of periodontitis were comparable between RA patients and control individuals, but the surface of healthy pocket epithelium (PESA) was significantly smaller in RA patients.

Serum Laboratory Markers in RA Patients and Controls According to Periodontal Status

RA patients with severe periodontitis had a significantly lower plaque score and tended to be older than RA patients with no, mild or moderate periodontitis. There was a tendency towards higher hsCRP levels in RA patients with severe periodontitis. Low education level was more common among RA patients with severe periodontitis (Table 2). None of the above mentioned differences or tendencies was found in controls (Table 3).

DISCUSSION

The prevalence of moderate to severe periodontitis in RA patients in the current study is fairly high (71%), but similar to those reported in other studies[2, 8]. However, the prevalence of moderate to severe periodontitis in controls was also high (69%) and not significantly different. Likewise, some other studies reported no significant differences in periodontitis prevalence between RA patients and controls[10-14], which also might be (partly) due to the potent anti-inflammatory medications used by the RA patients[15, 16]. The vast majority of studies did find a higher prevalence of periodontitis in RA patients as compared to controls[2, 6-8], It has to be noted that the patients in these studies, like in our study, were taking anti-inflammatory drugs. Furthermore, an association between periodontitis and RA also has been shown in animal studies[29, 30]. Both human and animal studies point towards an association between periodontitis and RA that might be due to sharing similar inflammatory markers, viz.

increased cytokines, matrix metalloproteinase and c-reactive proteins[31, 32]. This association is also in line with results from animal studies, showing that induction of arthritis in rats resulted in an increased periodontal breakdown, and that expression of an endogenous inhibitor of host-derived metalloproteinases (MMPs), viz. tissue inhibitor of MMPs (TIMPs) reduces the severity of periodontitis. Also in human studies, such a possible beneficial effect of TIMPs is shown[33, 34]. E.g., O'Dell et al[33] showed that systemically administration of a TIMP (subantimicrobial-dose doxycycline), FDA-approved for periodontitis, reduced the severity of RA in these patients. Administration of this TIMP to patients with severe cardiovascular disease was found to significantly reduce CRP, interleukin (IL) 6 and MMP-9 in peripheral blood[34].

Given the above mentioned, our findings might well be explained by the use of potent anti-inflammatory medication in RA patients. RA and chronic and aggressive periodontitis are chronic inflammatory disorders characterized by deregulation of the host inflammatory response. Increased secretion of pro-inflammatory mediators results in soft and hard tissue destruction of the synovium and periodontium respectively. Both diseases share risk factors and have pathological pathways in common, resulting in loss of function and disability as a final clinical outcome[35]. As such, drugs used for RA have also been reported to reduce periodontitis severity[11, 15, 16]. About eighty percent of the RA patients in our study were on corticosteroids (Table 1). Corticosteroids have anti inflammatory activities by inhibiting proinflammatory proteins as cyclooxygenase 2, IL-1, IL-2 and IL-6, tumour necrosis factor alpha and adhesion molecules[36]. About three-quarter of our RA patients used NSAIDs which have anti-inflammatory activity inhibiting cyclooxygenase, an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and tromboxanes. NSAIDs also have been shown to reduce alveolar bone loss in periodontitis[37]. A high number of RA patients (Table 1) also used disease modifying anti-rheumatoid drugs (DMARDs) such as methotrexate, sulfasalazine, chloroquine, leflunomide. These drugs are taken to reduce the inflammatory component in RA. Methotrexate in combinations with prednisolone decrease blood levels of Il-1β and IL-6 and inhibits the intensity of free radical-mediated processes in RA[38], which also may decrease periodontal inflammation.

While the periodontal inflamed surface area (PISA) was comparable between RA patients and controls (Table 1), the surface area of healthy pocket epithelium (PESA) was significantly lower in RA patients pointing towards more severe periodontitis in RA patients. Furthermore, the fact that there is not a significant difference between prevalence of periodontitis between RA patients and controls also might be due to the remarkably high periodontitis prevalence in our Indonesian controls. This is not surprising, as the prevalence of periodontitis in Indonesian general population may, depending on the definition used, be as high as 80%[39].

BMI may also have obscured an association between periodontitis and RA. Ideally, controls should also have been matched for BMI as fat tissue may cause a chronic, low-grade systemic inflammatory response that influences the level of CRP[40]. However, the randomly selected controls had on average a higher BMI. The higher BMI of controls compared to RA patients has been reported previously in a study that study failed to show BMI as a significant predictor of periodontitis in RA patients[8]. In another study BMI was statistically associated with missing teeth, PD and plaque index, but again not with CA loss, gingival index or periodontitis[41].

Noteworthy is the fact that there was a tendency towards higher hsCRP levels in RA patients with moderate to severe periodontitis compared to those with no/mild periodontitis (Table 2). Other studies also found higher levels of hsCRP in RA patients with periodontitis[2, 7]. No significant difference in hsCRP was observed between controls with periodontitis and controls without periodontitis (Table 3). Two main explanations can be given for these

findings. Firstly, periodontitis may aggravate RA since periodontitis is accompanied by higher CRP levels[42-46]. The elevation of inflammatory cytokines (such as IL-1, IL-6) that are locally induced by periodontitis[47] is thought to induce systemic inflammation by increasing serum CRP levels and thus to contribute to an increased systemic inflammation in RA[48]. Secondly, RA may aggravate periodontitis. Since more severe RA is also accompanied by higher CRP levels[48, 49], higher CRP levels may be a reflection of active RA, which may contribute to an increased inflammatory state in periodontitis. Interestingly, CRP level reduces in RA patients after periodontal therapy[20], lending support to the hypothesis that periodontitis may contribute to an increased systemic inflammation in RA.

Another explanation of higher CRP levels in RA patients with moderate to severe periodontitis compared to RA patients with no/mild periodontitis may be confounding by impaired maintenance of oral hygiene, smoking and low education level. Regarding oral hygiene, RA affects the wrist joint and the small joints of the hand. The joint afflictions may impair motor function of the hand and as a result may impair maintenance of proper oral hygiene resulting in periodontitis[50]. However, RA patients with moderate to severe periodontitis had lower mean plaque score than RA patients with no/mild periodontitis (Table 2). Therefore, impaired maintenance of oral hygiene in RA patients has probably not confounded the association between periodontitis and higher hsCRP levels.

CONCLUSION

Prevalence and severity of periodontitis in Indonesian RA patients is comparable to controls, but with less healthy pocket epithelium than in controls and a tendency of a higher inflammatory state in RA patients with severe periodontitis. Future research should focus on whether periodontitis contributes to the increased inflammatory state observed in RA patients with periodontitis, and whether periodontitis thereby contributes to increased severity of RA.

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Table 1.

Characteristics of and differences between RA patients and controls.

Variable		RA patients (N=75)	Controls (N=75)	Mean difference (sd)	p‖
Women	N(%)	60 (80%)	60 (80%)		
Smoking	N(%)	5 (7%)	5 (7%)		
Age (years)	Mean (sd)	46.5 (11.3)	46.9 (11.2)	0.4 (1.3)	0.015†
Education (low)	N(%)	45 (60%)	43 (57%)		0.868‡
Java origin(yes)	N(%)	63 (84%)	65 (87%)		0.815‡
BMI (kg/m^2)	Mean (sd)	22.5 (3.7)	24.1(3.6)	1.6 (5.0)	0.005†
Plaque score (%)	Median (iqr)	97 (94; 99)	95(90; 98)		0.023§
Number of teeth	Median (iqr)	26 (22; 29)	28 (25; 29)		0.034§
Periodontitis severity:					
PESA (mm^2)	Median (iqr)	825.0 (676.1; 944.3)	892.1 (786.4; 1040.1)		0.008§
PISA (mm^2)	Median (iqr)	98.7 (43.2; 179.4)	98.6 (35.3; 221.6)		0.669§
Number of sites:					
-CA loss≥3	Median (iqr)	22 (9; 44)	32 (14; 54)		0.099§
-CA loss≥4	Median (iqr)	5 (1; 18)	4 (1; 17)		0.998§
-CA loss≥5	Median (iqr)	0 (1; 6)	0 (0; 4)		0.666§
-CA loss≥6	Median (iqr)	0 (0; 2)	0 (0; 1)		0.890§
-PD≥4	Median (iqr)	1 (0; 5)	2 (0; 6)		0.638§
-PD≥5	Median (iqr)	0 (0; 1)	0 (0; 1)		0.734§
-PD≥6	Median (iqr)	0 (0; 0)	0 (0; 0)		0.963§
-BOP	Median (iqr)	11 (6; 21)	10 (4; 25)		0.951§
PD (mm)	Mean(sd)	1.7 (0.4)	1.8 (0.4)	0.1 (0.6)	0.205§
CA loss (mm)	Mean(sd)	2.0 (0.8)	2.1 (0.8)	0.0 (1.1)	0.930§
Periodontitis prevelance‖:					0.547§
-No mild	N(%)	22 (29%)	23 (31%)		
-Moderate	N(%)	37 (49%)	40 (53%)		
-Severe	N(%)	16 (21%)	12 (16%)		
Biomarkers:					
ACPA igG (RU/ml)	Median (iqr)	1.2 (0.0; 46.2)	0.0 (0.0; 0.0)		<0.001§
ESR (mm/hour)	Median (iqr)	36 (18; 53)	22 (13; 35)		0.001§
hsCRP (mg/l)	Median (iqr)	4.8 (1.7;17.1)	1.1 (0.6; 2.9)		<0.001§
Medication:					
Corticosteroid(prednisolone)	N (%)	60 (80%)	0 (0%)		
NSAIDs	N(%)	55 (73%)	0 (0%)		
Methotrexate	N(%)	52 (69%)	0 (0%)		
Cloroquine	N(%)	36 (48%)	0 (0%)		
Leflunomide	N(%)	7 (9%)	0 (0%)		
Sulfasalazin Antihypertensives Birth control pills	N(%) N(%) N(%)	6 (8%) 5 (6%) 0 ()%)	0 (0%) 6 (8%) 1 (1%)		

Data were analyzed pair wise. * p=probability, †paired t-test, ‡McNemar test, §Wilcoxon Signed rank test, ‖ Criteria of Page and Eke[23]; ‖:

Table 2.

Biomarkers and characteristics of RA patients according to periodontal status.

Variable	No or mild Periodontitis(n=22)		Moderate Periodontitis(n=37)		Severe Periodontitis(n=16)		p*
	Median	IQR	Median	IQR	Median	IQR	†
Age (years)	44.0	(34.0; 54.0)	49,0	(38.5; 54.0)	50.5	(42.5; 55.8)	.255
BMI (kg/m^2)	21.8	(19.6; 26.3)	22.2	(19.8; 25.2)	22.6	(20.2; 24.6)	.981
Plaque score (%)	98.0	(96.0; 99.0)	97.0	(95.0; 98.0)	92.5	(91.0; 97.5)	.010
ACCP IgG (RU/ml)	1.3	(0.0; 46.1)	0.0	(0.0; 31.6)	1.6	(0.0; 78.4)	.612
ESR (mm/hour)	29.0	(17.0; 38.0)	36.0	(18.0; 60.0)	41.5	(24.0;69.5)	.257
hsCRP (mg/l)	4.1	(2.6; 5.4)	3.3	(0.8; 24.9)	15.4	(6.3; 21.8)	.063
Years RA	5.0	(2.0; 10.0)	4.0	(2.0; 6.0)	3.0	(1.5; 5.0)	.301
	%	n	%	n	%	n	‡
Sex (woman)	86	19	84	31	63	10	.105
SES (low)	41	9	68	25	69	11	.064
Smoking (yes)	0	0	8	3	13	2	.192
RF (yes)	36	8	16	6	38	6	.883

%: column percentage. n: number; *p: probability; RU: relative unit; †Differences in medians are tested using Kruskal-Wallis test. ‡Difference in percentages are tested using chi- square analyses, linear by linear association, method exact in case of lack of expected cell count.

Table 3.

Biomarkers and characteristics of controls according to periodontal status.

Variable	No or mild Periodontitis(n=23)		Moderate Periodontitis(n=40)		Severe Periodontitis(n=12)		p*
	Median	IQR	Median	IQR	Median	IQR	†
Age (years)	48.0	(39.0; 54.0)	44.5	(38.5; 54.0)	50.0	(44.5; 56.0)	.429
BMI (kg/m^2)	23.2	(20.6; 25.3)	23.7	(22.2; 27.0)	24.6	(20.3; 30.7)	.448
Plaque score (%)	97.0	(95.0; 99.0)	94.0	(90.0; 98.0)	93.0	(80.0; 96.5)	.127
ACCP IgG (RU/ml)	0.0	(0.0; 0.0)	0.0	(0.0; 0.0)	0.0	(0.0; 0.0)	.959
ESR (mm/hour)	20.0	(12.0; 26.0)	25.5	(13.0; 35.5)	21.0	(16.0; 36.0)	.640
hsCRP (mg/l)	0.9	(0.6; 1.3)	1.2	(0.5; 3.8)	2.4	(0.6; 3.7)	.273
	%	n	%	n	%	n	‡
Sex (woman)	78	18	78	31	92	11	.522
Smoking(yes)	4	1	8	3	8	1	.734
SES (low)	74	17	50	20	50	6	.103
RF (yes)	9	2	0	0	0	0	.115

%: column percentage. n: number; *p: probability; RU: relative unit;†Differences in medians are tested using Kruskal-Wallis test. †Difference in percentages are tested using chi- square analyses, linear by linear association, method exact in case of lack of expected cell count.

* Dentsply, London, United Kindom

† Immulite 2000™, Diagnostic Products Corp., Los Angeles, CA, USA

‡ ELISA; Euroimmun™, Medizinische Labordiagnostika AG, Germany